REMARKS

Claims 67 and 168-182 were pending prior to this Amendment. This Amendment cancels claims 67, 172-176, 181 and 182. It adds Claims 183-206. Accordingly, the pending claims are 168-171, 177-180 and 183-206.

Amendments adding reference molecules to Claim 168 and 169

The basis for reference molecules in the kits of Claims 168 and 169 can be found at page 27, lines 11-14. The fragments of interest in claim 168 correspond to those disclosed, for example, in Claim 6 of the application as filed. The fragments of interest in Claim 169 correspond to those disclosed, for example, in Claims 9 and 11 as filed. ("Oligomerization domain", listed in Claim 9, is omitted from Claim 169, as that domain is normally considered to be within the region of inter-chain disulfide bonds cited elsewhere in Claim 169).

New Claims 183-191

Claim 183 finds the basis for its two binding agents in the specification at page 16, lines 4-10, in combination with the definition of an epitope, page 15, line 33 – page 16. line 1.

The fragments of interest in claim 184 correspond to those disclosed, for example, in Claim 1 of the application as filed.

The fragments of interest in claim 185 correspond to those disclosed, for example, in the specification at page 29, lines 15-17 as well as the disclosure of the 20 kDa lower limit, for example, in the specification at page 2, lines 26-30 and Claim 1 as filed

The fragments of interest in claim 1 correspond to those disclosed, for example, in Claim 6 of the application as filed.

The fragments of interest in claim 187 correspond to those disclosed, for example, in Claim 6 of the application as filed.

The fragments of interest in Claim 188 correspond to those disclosed, for example, in Claims 9 and 11 as filed.

The basis for the reference molecules in dependent claims 189-191 is found in the application at page 27, lines 11-14, and for Claims 190 and 191, also the portions of the specification and claims as filed defining which portions of thrombospondin are the sources of the fragments of interest. Claims 190 and 191 parallel Claims 168 and 169, respectively, which are discussed above as to the reference molecules.

New Claims 192-194

These dependent claims are for kits that further comprise a means for minimizing platelet activation and/or protease activity. In Claim 192, the means are selected from the group consisting of a device for separation of plasma (for support, see page 20, lines 23-28 especially item (6); heparin (see page 20, line 32), a heparin fragment (see page 30, line 32), a protease inhibitor (see page 20, line 31), a platelet inhibitor (see page 21, line 9) , and a clotting inhibitor (see page 21, line 9). In Claims 193 and 194, less than all of the foregoing options are in the group.

New Claims 195-196

There is support throughout the specification for using an antibody as the binding agent.(See for example, pages 6-10; page 14, lines 13-27, page 47, lines 11-13.)

New Claims 197-198

These two claims parallel Claims 168 and 169, respectively. A difference is that, in Claims 197 and 198, the following appears: "a reference molecule, said molecule comprising a target to which the binding agent binds, said target being one that is present in a plasma thrombospondin fragment" Support for including such specificity in the definition of the reference molecule can be found throughout the application, which describes inventions directed at measuring thrombospondin levels.

New Claims 199-204

These dependent claims include language from, and therefore have the same basis as, dependent claims 170, 171, 192, 193, 194 and 195, respectively.

Rejection of Claims 67 and 168-182 under 35 U.S.C. 112, first paragraph (Paragraph 4 of the Office Action)

The Examiner has rejected these claims because the specification does not "identify a plethora of agents other than an antibody that binds thrombospondin fragments." (Page 4 of the Office Action). In support of the rejection the Examiner has cited *Vas-Cath*, *Fiers v. Ravel*, *Amgen v. Chugai*, and *Regents of the University of California v. Lilly*. This rejection is traversed

on the grounds that follow:

Applicant respectfully states that the court opinions cited by the Examiner do not provide the appropriate guidelines for assessing Applicant's claims. Applicant's claims specify kits wherein the invention lies in significant part in the recognition of what the specificity of the binding agents should be: Those binding agents that bind epitopes located within plasma thrombospondin fragments. In contrast to the court opinions cited by the Examiner, the Applicant in his application demonstrated a clear precise conception of his invention, thereby satisfying the written description requirement. The invention does not reside in whether an antibody or other type of binding agent is used. A person of ordinary skill in the art who wishes to avail himself of Applicant's invention can either use binding agents specified by Applicant, use methods specifically described by Applicant to obtain other binding agents of desired specificity, or use other established procedures in the literature to obtain them. (Binding agents are discussed for example at page 14, lines 13-27; page 23, line 1 – page 26, line 6). The key is that Applicant has defined, with sequence specificity, the target(s) to which the binding agent must bind. Given that knowledge, a person of ordinary skill can screen for a binding agent of any type.

The court opinions cited by the Examiner deal with lack of knowledge of the protein/nucleic acid sequence of interest:

Vas-Cath v. Mahurkar, 935 F. 2d 1555, (CAFC 1991), clarifies that, in general, the written description requirement and the enablement requirement are separate from each other. More specifically, in *Fiers v. Ravel*, the single count in an interference proceeding was essentially to a specific DNA sequence, one coding for a specific interferon polypeptide. The

court ruled that the inventor did not know the specific sequence and therefore did not meet the written description requirement. (In the present case, Applicant specifically specifies the polypeptide sequences of significance to his inventions). Similarly, in *Amgen v. Chugai*, the pertinent claims were to a purified and isolated DNA sequence and the inventor did not know the precise sequence at the time of filing the application. Also similarly, In *Reagents of the University of California*, the Court held that a description of a particular cDNA, rat insulin cDNA, was not a description of the cDNAs of two claimed broader classes.

In view of the foregoing, the use of the term "binding agent" in Applicant's claims does not prevent any of his claims from meeting the written description requirement.

Rejection of Claims 168, 169-172 and 176-178 under 36 U.S.C. 112, second paragraph. (Paragraph 7 of the Office Action)

Claim 168 is rejected as reciting amino acid residues such as I-165, without reciting a corresponding amino acid sequence (and SEQ ID No.) which contains such a residue. In response, Applicant has amended Claim 168 to specify SEQ ID No. 38 and where the amino acid residues are referred to therein. SEQ ID No. 38 is set forth in the application at page 32, lines 18-39 (and in the Sequence Listing for this case), and as being the amino acid sequence of human thrombospondin-1 (See application at page 33, line 14.)

The amino acid numbers that appeared in Claim 168 prior to amendment were 165, 263, 792 and 982, corresponding to the numerical portions of I-165, V-263, R-792 and Y-982, respectively. (The letters, I, V, R, and Y correspond to the one-letter amino acid abbreviations;

see Specification at page 12, lines 15-16). The numbering system used in Claim 168 was based on "mature thrombospondin"; i.e. thrombospondin in which the signal peptide had been removed. (See, application at page 33, line 1-4). Because the signal peptide is assumed in the application to be 18 amino acids, the amino acid numbers referred to in claim 168 were smaller than their number within sequence ID NO: 38, the sequence for the full human thrombospondin sequence; i.e., the signal peptide had not been removed. The amendment to Claim 168 takes that into account.

It can be noted that the signal peptide could be as large as 22 residues instead of 18 residues (application at page 33, line 1-4), but, as will be seen below, that would not significantly affect the discussion here.

Claim 169 is rejected as lacking antecedent basis for the recitation "the TSP Ab-4 antibody" in the last line of the claim. Applicant has deleted that term from the claim.

The remaining still-pending claims cited in this rejection are dependent on Claims 168 and/or 169 and an amendment to those dependent claims to overcome this rejection does not appear to be necessary,

Rejection of Claims 67 and 168-176 under 35 U.S.C. 102(b) as being anticipated by WO 98/07035) (Paragraph 9 of the Office Action)

These claims have been rejected on the grounds that the WO document, in its abstract and the bridging paragraph of pages 11-12, discloses a kit including antibodies that detect thrombospondin fragments in a body fluid. The Examiner states that the antibodies are disclosed

as cross-reacting with 67-80 kDa and 20 kDa fragments of thrombospondin-1 (Page 7, second paragraph and page 9, first full paragraph are cited). It is the Examiner's position that, absent evidence to the contrary, the disclosed thrombospondin contains a domain and/or portion within the protease-resistant core of thrombospondin, said domain being selected from the group consisting of a domain of inter-chain disulfide bonds, an oligomerization domain, a procollagen-like domain, a type 1 repeat, a type 2 repeat, and a type 3 repeat, a portion of a collagen type V domain and an epitope for binding TSP Ab-4 antibody. (Applicant has, by amendment, removed the reference to the TSP Ab-4 antibody.)

This rejection is traversed on the grounds that follow.

Applicants kit claims no longer specify a single antibody as the single item that the kits must comprise. They must, as a result of amendments, now further comprise a reference thrombospondin fragment and, in some of the dependent claims, a means of reducing thrombospondin release from platelets and degradation during the plasma collection and/or post-collection process. The reference fragments corresponds to region(s) of thrombospondin that appear in plasma fragments.

The addition, to some claims, of the requirement for a means to reduce thrombospondin release from platelets and degradation is of particular significance in the case of Applicant's invention. In contrast to prior art, which discloses measurements of thrombospondin levels and/or both thrombospondin and fragment levels, Applicant's inventions seek to measure thrombospondin fragment levels while minimizing input from thrombospondin.

Independent of the above considerations, which by themselves should overcome the rejection based on the WO document, Applicant points to the following deficiencies of the WO

document as regards its relevance to the present application:

The Examiner states that the WO document discloses its antibodies as cross-reacting with a 67-80 kDa thrombospondin fragment and cites page 7, second paragraph and page 9, first full paragraph. These paragraphs disclose, however, that the antibodies react with the 67-80 kDa fragment of COMP, not with the 67-80 kDa fragment of thrombospondin. For example, on page 7, it is stated that, "These antibodies also cross react with another group of COMP C-terminal degradation fragments which have a molecular weight of from about 67 kDa to about 80 kDa..."

The Examiner also states that the antibodies disclosed in the WO document cross-react with the 20-Da fragment of thrombospondin-1; i.e., the N-terminal 20-kDa fragment of thrombospondin. (See WO document at page 5, lines 7-8 and page 7, eighth line from the bottom of the page). However, an epitope within the N-terminal 20 kDa fragment would not be located within the portion of mature thrombospondin extending from amino acid I-165 to amino acid Y-982, as specified in Claim 168. This can be seen from the following considerations.

As regards Claim 168: There are **164** N-terminal amino acids that fall outside the range from amino acids I-165 to Y-982 in mature thrombospondin. Therefore the fraction of the total number of amino acids, **1152**, that fall outside the I-165 to Y-982 range at the N-terminal end is **164/1152**. The molecular weight of mature thrombospondin is 185 kDa. (See specification at page 1, lines 18-21.) Therefore, the molecular weight of the N-terminal region falling outside the I-165 to Y-982 range can be estimated by multiplying 185 kDa by **164/1152**, which results in **26.3 kDa**. (Alternatively, if one assumes that the removed signal peptide is 22 amino acids, rather than 18 amino acids, - see specification page 33, lines 1-2 – then the calculation results in a molecular weight of 25.8 kDa). A similar estimate is obtained for the 164-amino acid N-

terminal segment if one uses the web site http://bioinformatics .org.sms/prot_mw.html referred to on page 4, lines 8-11, of the application. (The web site calculates the molecular weights of the polypeptide component (without glycosylation) of the 164-amino N-terminal segment to be 14.07 percent of that of thrombospondin. If one assumes that, on the average, the 164-amino acid N-terminal segment and thrombospondin are similarly glycosylated, the 164-amino acid N-terminal segment would have a molecular weight of 26.0 kDa (equal to 14.07 percent of 185 kDa)).

In summary, the 164 amino acid N-terminal segment outside the I-165 to Y-982 range specified in Claim 168 would be expected to be about **26 kDa**. Therefore, a **20-kDa** N-terminal fragment disclosed in the WO document, being significantly smaller than 26 kDa, would not be expected to extend all the way to, or beyond, amino acid I-165. Therefore the disclosed 20-kDa N-terminal fragment would not be expected to have an epitope required by Claim 168, namely one from the portion of thrombospondin extend from amino acid I-165 to amino acid Y-982.

As regards Claim 169: Applicant notes, preliminarily, that the claim has been amended to include the phrase "and wherein the binding agent binds to an epitope within said region".

Pertinent to the rejection in view of the WO document, that rejection is traversed based on reasoning similar to that above for the traversal of the rejection of Claim 168. The thrombospondin regions cited in Claim 169 are located within the region of thrombospondin cited in Claim 168, amino acids I-165 to Y-982. Indeed, the N-terminal ends of the regions recited in Claim 169 are even more distant from the N-terminal fragment of thrombospondin than amino acid I-165 is. This can be seen by reference to Table 1 below:

Table 1

Domain	Amino acid number range, in mature thromobospondin, covered by the Domain	Cited in application
inter-chain disulfide bonds	241-262	11:9-13
procollagen-like domain	263-360	11:13
type 1 repeat	361-530	11:14
type 2 repeat	531-673	11:14
type 3 repeat	698-925	11:16
collagen type V domain	333-412	12:14-15

Accordingly, the 20 kDa N-terminal fragment disclosed in the WO document would not be expected to have an epitope required by Claim 169.

Additionally, there is data in Applicant's application indicating that the 20-kDa N-terminal fragment disclosed in the WO document is not the same as a 20 kDa plasma fragment referred to in Applicant's claims. Specifically, in contrast to the 20 kDa fragment disclosed in the WO document, the plasma fragments in Applicant's claims do not extend all the way to the N-terminal end of thrombospondin. This can be seen by considering data, in Applicant's application, on the reaction of antibody Ab-4, as follows:

Applicant's application discloses that his data showed that the Ab-4 antibody reacts with the 20 to 35 kDa plasma fragment (as well as the other two major fragments). (See Application at Page 6, lines 12-15). It also discloses that the epitope recognized by the Ab-4 antibody has been reported to be within the collagen type V binding domain, a domain reported to extend from

amino acid 333 to amino acid 412. (Application at page 12, lines 14-15). Amino acid 333 is too far from the N-terminal end of thrombospondin to overlap an N-terminal 20-kDa fragment. The N-terminal 20-kDa fragment would be expected to be about 125 amino acids in size ("125" is obtained by multiplying 1152 by 35 kDa/185 kDa according to reasoning similar to that used above in connection with Claim 168.). That would not be large enough to extend from the N-terminal end of thrombospondin to amino acid number 333.

In view of the foregoing, 168 and 169 (and their dependent claims) are neither anticipated by nor made obvious by, the WO document.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for initial examination and allowance, the Examiner is invited to phone Applicants' undersigned attorney at **610-724-2952**.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

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By Allan H. Fried

Allan H. Fried
Registration No. 31,253
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.